Urethral function in overactive bladder syndrome

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CHAPTER 5

EXPLORATORY ANALYSIS OF THE EFFECT OF MIRABEGRON ON URODYNAMIC SENSATION PARAMETERS AND URETHRAL PRESSURE VARIATIONS

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INTRODUCTION

Urinary continence requires a coordinated function of the bladder as a low pressure reservoir while the outlet resistance is maintained by the urethra.]In storage phase, sympathetic and pudendal nerve activity are responsible for this.. When voiding is initiated, sympathetic stimulation is inhibited and parasympathetic activation results in the contraction of the detrusor muscle and in relaxation of the urethra[1]. Patients with overactive bladder syndrome (OAB) have symptoms of frequent voiding and the sudden need to void, with or without urinary incontinence[2]. OAB is a very common problem with a negative impact on health-related quality of life[3-5].]This condition is often idiopathic, with no responsible anatomical substrate. Urodynamic testing is used to evaluate bladder function in these patients. Detrusor overactivity can be demonstrated during filling cystometry in these patients, but in asymptomatic patients as well. The involuntary initiation of voiding phase can lead to urge urinary incontinence. Research on OAB so far, has mainly been focused on detrusor dysfunction and less on the potential contribution of urethral function. A sudden fall in urethral outlet resistance due to urethral pressure variations (UPV) could result in stimulation of urethral afferents by leakage of urine into the urethra, thereby causing OAB as well[6, 7]. Urge urinary incontinence only due to a sudden fall in urethral pressure has in the past been defined by the International Continence Society (ICS) as urethral instability (URI). Because of the rarity of this condition and lack of consensus about the clinical importance of this phenomenon, the definition was never adjusted and no longer included within ICS terminology and definitions. A recent systematic review on URI concluded however that URI may be regarded a potential pathophysiological entity of its own within cohorts of patients with OAB[8]. This was supported by a recent report based on a literature review and discussions during the ICI-RS meeting on urethral function in 2014[9]. In addition, a recent review underlined the importance of identifying subgroups of patients within OAB to optimize tailor treatment and improve outcomes[10]

Medical treatment options for the management of OAB consists of oral antimuscarinics and a beta 3 adrenoceptor (B3AR) agonist (Mirabegron). Treatment with antimuscarinics result in reduction of voiding frequency, urgency episodes and/or urgency urinary incontinence[11]. However, treatment persistence is low, mainly because of bothersome side effects, with around 30% of patients continuing therapy after one year[12-14].

Past research demonstrated that antimuscarinics had no significant influence on static urethral urethral closure function[15, 16].

Mirabegron is approved for the treatment of overactive bladder symptoms in the last decade. It has been proven clinically and urodynamically effective in the treatment for OAB[17, 18]. The effect of mirabegron on the urethral pressure and on urethral pressure variations during filling cystometry is however unknown. In addition, the presence of B3AR was recently demonstrated in the human female urethra[19]. The aim of this study was to assess the influence of the B3AR agonist mirabegron UPV during urodynamic investigation and the association of symptoms and voiding diary data before and on treatment.

MATERIALS AND METHODS

Between May 2015 and May 2018 consecutive female patients with OAB symptoms for whom conservative therapy was unsuccessful enrolled in this prospective study. The study was performed in two centers in the Hague. Ethical committee approval was granted and all patients provided written informed consent. Inclusion criteria were female, >18 years of age, mentally fit to consent, bothersome OAB symptoms, voiding diary with total urine production in 24 hours < 2200ml, willing to stop medication for lower urinary tract (LUT) dysfunction 2 days before urodynamic investigation at entry of the study and willing to start mirabegron after initial urodynamic investigation. Exclusion criteria were cystocele POP-Q stage 2 or more, necessity to perform CIC or significant post void residual volume (> 100ml),; bladder outlet obstruction or underactive or acontractile detrusor, unwilling or unable to stop current treatment for LUT dysfunction, treatment with intravesical botulinum toxin A less than one year before investigation and contra indications for using mirabegron. All women underwent clinical evaluation, including history and physical examination. Urinary tract infection was excluded and a cystoscopy was performed to rule out bladder neoplasm. At entry of the study patients were evaluated with a voiding diary, two validated questionnaires for the Dutch language and an urodynamic investigation. The used questionnaires were the Urogenitary Distress Inventory (UDI-6) and the Incontinence Impact short form (II-Q). Cystometry was carried out in a semi-upright sitting position with a continuous filling rate of 30-40ml/min. After urodynamic investigation, patients started with a daily

dosis of 50 mg mirabegron and six weeks later, a second evaluation was performed with a voiding diary, the same questionnaires and urodynamic investigation. The urodynamic investigations were performed with a dual-air balloon sensor urodynamic catheter (Laborie T-DOC® air-charged dual sensor catheter, distance from bladder sensor to urethral sensor 6cm, shore hardness 65±5D, 7Fr), positioned at maximum urethral pressure. During filling cystometry, the sensory markers first sensation of filling (FSF), normal desire (ND) and strong desire (SD) and maximal filling capacity (MMC) were marked. Pelvic floor electromyography (EMG) was performed with surface patch electrodes. URI was defined as UPV exceeding 30 cmH2O. The main endpoint was defined as the number of patients with a reduction of UPV on urodynamic investigation while on treatment with beta 3 adrenoreceptor agonist. The secondary endpoints were individual differences in urethral pressure before and on treatment and to explore association of symptoms before and on treatment with mirabegron. A McNemar test power analysis was performed. A sample size of 60 patients was calculated. Statistical analysis was performed with SPSS statistics (IBM, version 23). Data were analyzed using descriptive statistics and Wilcoxon test for paired samples.

RESULTS

Fifty-one patients were eligible, of which forty-nine patients underwent complete evaluation at entry. Flowchart of the study population is shown in figure 5.1. Two patients cancelled all further appointments and were lost to follow-up after inclusion. Forty-two patients completed the study with two urodynamic investigations. One patient discontinued because of side effects of mirabegron (tachycardia). One patient withdrew participation because eventually she did not want to use medication at all, one patient was referred for pelvic muscle floor training based on the results of her urodynamic evaluation, one patient had an urinary tract infection after the first urodynamic investigation and did not want a second urodynamic investigation and one patient was withdrawn because of her language barrier. Two other patients were lost to follow up. Two patients used antimuscarinics at entry of the study and discontinued use at least 2 days before urodynamic evaluation.

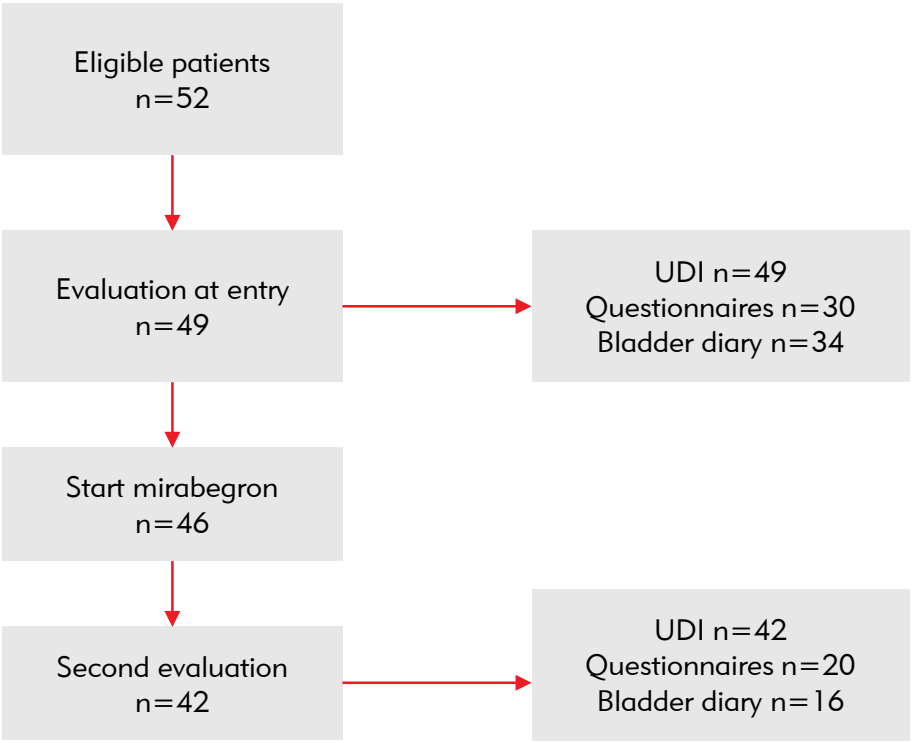

Figure 5.1 Flowchart of study population

Prevalence of URI was in 15 patients (31%) at initial urodynamic investigation, and in 8 patients (19%) at second investigation. DO was present in 9 patients (18%) at initial urodynamic investigation, and in 11 patients (26%) at second investigation. In figure 5.2, an example of urodynamic tracing in a patient with URI, before and after treatment with mirabegron is shown.

Since the aim of our study was to assess the influence of a B3AR agonist on urethral pressure variations we performed a separate analysis of patients with and without URI. The analysis of these subgroups was performed only in patients who completed both urodynamic studies, so that they could serve as their own control. Results of the urodynamic parameters for the complete cohort and subgroups are shown in table 5.1. The difference in maximal and minimal urethral pressure was significantly changed in the URI-group and not in non URI-group after treatment with mirabegron.

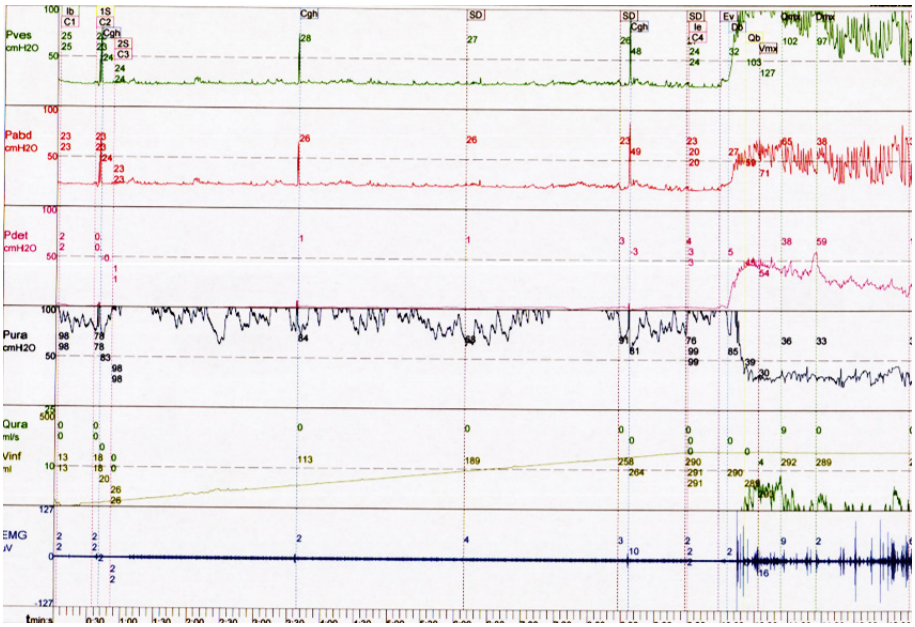

Figure 5.2a Filling cystometry in patient with URI before treatment with mirabegron

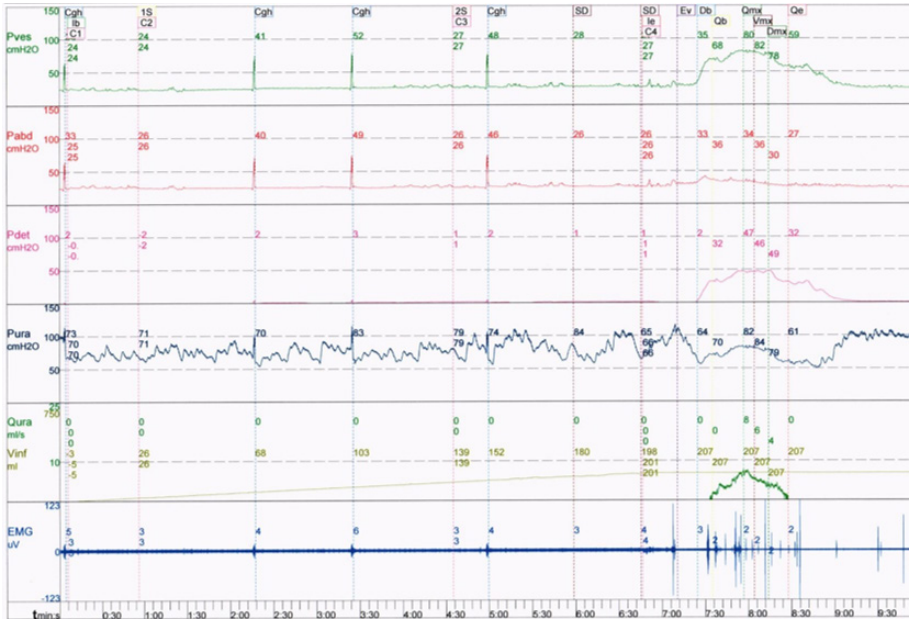

Figure 5.2b Filling cystometry in the same patient aftertreatment with mirabegron

Table 5.1 Urodynamic parameters before and after mirabegron

	Urodynamic parameters – average (range)								
	All patients - before mirabegron (n= 42)	URI-patients –before mirabegron (n=15)	Non-URI-patients – before mirabegron (n=27)	All patients – after mirabegron	URI-patients – after mirabegron	Non-URI-patients – after mirabegron	P-value – all patients	P-value – URI-patients	P-value – Non-URI-patients
Bladder capacity (ml)	303 (85-662)	340 (130-662)	279 (85-495)	330 (0-661)	392 (161-661)	292 (0-561)	0.066	0.087	0.354
Residue (ml)	44 (0-307)	8 (0-307)	10 (0-233)	66 (0-535)	15 (0-421)	11 (0-535)	0.823	0.722	0.987
First desire (cm H2O)	112 (16-288)	71 (16-258)	77 (16-288)	151 (13-372)	208 (32-372)	110 (13-305)	0.023*	0.005*	0.416
Normal desire (cm H2O)	192 (50-459)	182(58-456)	175 (50-459)	231 (49-478)	298 (97-450)	190 (49-478)	0.008*	0.010*	0.087
Strong desire (cm H2O)	267 (74-580)	321 (131-580)	236 (74-495)	302 (57-620)	379 (159-620)	238 (57-526)	0.016*	0.046*	0.141
Qmax (ml/s)	21.8 (1.9-341)	9.7 (1.9-341)	16.5 (4.1-31.9)	16.0 (4.2-40.5)	14.8 (7.7-40.5)	19.9 (4.2-34)	0.788	0.272	0.904
Qav (ml/s)	14.9 (0.9-188)	5.0 (2.9-188)	8.5 (0.9-29)	7.3 (0.3-21.5)	6.1 (0.3-21.5)	7.1 (2.2-20.1)	0.465	0.46	0.955
Max. urethral pressure (cm H2O)	95 (47-150)	95 (75-130)	89 (47-150)	86 (29-153)	90 (40-143)	90 (29-153)	0.150	0.099	0.368
Min. urethral pressure (cm H2O)	62 (25-110)	50 (26-110)	57 (25-109)	60 (16-130)	57(16-101)	58 (16-130)	0.918	0.196	0.659
Urethral pressure difference (cm H2O)	34(6-103)	40 (8-95)	24 (6-103)	26 (3-80)	25 (8-46)	24 (3-80	0.200	0.010*	0.745

Wilcoxon test for paired samples, $p < 0.05$ is significant

A striking finding is that in the URI group, the urodynamic sensation markers all improved while in the non URI-group, none of the sensation markers were changed.

For the entire group of patients, treatment with mirabegron resulted in a reduction of symptoms in the questionnaires on the domains of active relaxation (IIQ p=0,005, UDI-6 p=0,031) and emotional health (IIQ, p=0,011) and in frequency of small amounts urinary incontinence (UDI-6 p=0,011). Results are show in table 5.2. In the URI-group, treatment with mirabegron resulted in a reduction of leakage of drops urine and of urine leakage due to physical activity (UDI-6, question 3 and 4). Results are shown in table 5.3. In the non-URI group, there were no changes in the questionnaires.

In regard to urodynamic parameters, treatment with mirabegron resulted in an improvement of FSF(p=0,019), ND (p=0,015) and SD (p=0,020) demonstrated in urodynamic investigation. Bladder capacity was improved, but not significantly (p=0.07).

Unfortunately, only thirty-four patients adequately completed their voiding diary. After treatment, seventeen of these thirty-four handed in a second complete diary. We only performed analysis on these patients, so that they served as their own control. Results are shown in table 5.4. Voiding frequency improved on treatment with mirabegron, both during the day and in the night. Maximal functional capacity also improved.

Table 5.2 Results from questionnaires – all patients

Domain	Before mirabegron (n=17)	After mirabegron (n=17)	P-value
IIQ-7 Q1	1.18	0.47	***0.03***
IIQ-7 Q2	1.71	1.00	***0.01***
IIQ-7 Q3	1.35	0.88	0.09
IIQ-7 Q4	1.35	1.06	0.25
IIQ-7 Q5	1.19	0.82	0.11
IIQ-7 Q6	1.18	0.65	***0.03***
IIQ-7 Q7	1.38	1.12	0.45
UDI 6 Q1	2.00	1.56	0.25
UDI 6 Q2	1.65	1.44	0.59
UDI 6 Q3	1.12	0.75	***0.03***
UDI 6 Q4	1.76	1.13	***0.02***
UDI 6 Q5	1.00	0.75	0.23

Wilcoxon test for paired samples, $p < 0.05$ is significant

IIQ-7; Incontinence Impact Questionnaire short form, UDI 6; Urogenital Distress Inventory

Table 5.3 Results from questionnaires for patients with urethral instability

Domain	Before mirabegron (n=7)	After mirabegron (n=7)	P-value
IIQ-7 Q1	0.86	0.29	0.180
IIQ-7 Q2	1.57	1.29	0.317
IIQ-7 Q3	1.43	1.14	0.480
IIQ-7 Q4	0.71	1.00	0.414
IIQ-7 Q5	1.00	0.86	0.564
IIQ-7 Q6	1.00	0.71	0.414
IIQ-7 Q7	1.43	1.29	0.783
UDI 6 Q1	2.00	1.43	0.357
UDI 6 Q2	1.29	1.29	0.705
UDI 6 Q3	1.00	0.57	0.083
UDI 6 Q4	1.43	0.71	0.059
UDI 6 Q5	0.86	0.43	0.180
UDI 6 Q6	0.57	1.14	0.102

Wilcoxon test for paired samples, $p < 0.05$ is significant

Table 5.4 Results voiding diaries

N=17	Before mirabegron (avg (range))	After mirabegron (avg (range))	P-value
Voiding frequency day	9.6 (3-18)	7.71 (4-16)	0.034*
Voiding frequency night	1.3 (0-3)	0.9 (0-3)	0.047*
Maximal portion (ml)	298 (100-500)	324 (150-650)	0.001*
Average portion (ml)	186 (90-310)	211 (122-333)	0.136

Wilcoxon test for paired samples, $p < 0.05$ is significant

DISCUSSION

This is the first study to date presenting the effect of treatment with a B3AR agonist on continuous urethral pressure during filling cystometry. Previous studies have reported subjective efficacy and tolerability of treatment with mirabegron alone or in combination with solifenacin[20]. In 2016 Vecchiolo Scaldazza was the first to report urodynamic results of treatment with mirabegron or solifenacin in 60 patients with OAB [18]. Urodynamic parameters as first, normal and strong desire and continuous urethral pressure measurement were not mentioned and/or performed in aforementioned study.

The present study also demonstrates, in line with previous studies[17, 18], that treatment with mirabegron results in a significant improvement of symptoms and quality of life. In contrast to these studies, changes in bladder capacity and DO were not significant.

An important finding is that this study demonstrates that patients with URI have a different response to mirabegron than patients with the same clinical symptoms without URI.

Treatment with mirabegron had a significant effect on all sensation parameters during urodynamic investigation in patients with URI. The changes in first, normal and strong desire are of clinical importance, since these moments will determine when patients will look for a toilet in their daily lives, probably even more than the maximal bladder capacity. The difference in maximal bladder capacity before and on treatment was greater in the URI group, but this change was not statistical significant. The maximal urethral pressure decreased more than the minimal urethral pressure. The difference between maximal and minimal urethral pressure decreased significantly in the URI-group. However, some caution is required considering the loss of power. Theoretically, this could implicate that treatment with mirabegron could be beneficial in patients with high urethral pressure and/or UPV, while maintaining minimal pressure and thus stabilize UPV. UPV is a more common urodynamic phenomenon than detrusor overactivity, demonstrated in one third of the female patients at presentation with OAB in this study. Kirschner-Hermanns et al.[21] even reported a prevalence of 54% in a consecutive series of female patients and a prevalence of 79% in the subgroup of patients with OAB within this cohort, but this was with a lower cut-off value of pressure drops of 15cm H2O or more during filling cystometry.

The main limitation of this study is the small, underpowered sample size. At initiation the study in 2014, mirabegron was just approved for medical treatment of OAB in our country. As time went on, more patients already received mirabegron treatment from their general practitioner and were not willing to use it again for research purposes. In addition, the questionnaires and bladder diaries were unfortunately completed by a limited number of patients, which limits the correlation of urodynamic findings with clinical symptoms so caution is required in interpreting the results. Nevertheless it is important that, apart from prevalence, urodynamic effects of medical treatment are reported. Another limitation is the lack of results of an asymptomatic control group.

This is the first prospective clinical study comparing OAB patients with and without URI. Patients with URI have a different response on mirabegron than patients without OAB. In the past was already demonstrated that presence of URI was a better predictor of outcome in sacral nerve stimulation than DO[22]. The question remains if URI is a separate entity within OAB, or that it should be considered as a predictor for effectiveness of certain treatments. With current insights and recommendations on urethral function, the results of the present study contribute to optimizing treatment choices in patients with OAB. Future research should elucidate the correlation of experienced complaints with urodynamic parameters after treatment and confirm our results in a bigger cohort of patients.

CONCLUSIONS

In this small study we demonstrated that urethral pressure differences are significantly reduced by treatment with the beta 3 adrenoceptor agonist mirabegron in patients with URI. Although the prevalence of URI was reduced with 12% after six weeks of treatment, this difference was not significant. URI seems to have a predictive value in treatment choices for OAB. Taken into consideration the amount of studies performed to the effect and influence of different treatment modalities on detrusor overactivity in patients suffering from OAB, these results confirm the need for future research to the role of urethral function within OAB. We propose that the ICS will include URI again within her definitions and terminology.

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